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Continuous multi-step synthesis by extrusion - telescoping solvent-free reactions for greater efficiency

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Chemical manufacturing typically requires more than one step, involving multiple batch processes, which makes synthesis at scale laborious and wasteful. Herein, we demonstrate that several reactions can be telescoped into a single continuous process and/or be carried out as a continuous multi-component reaction (MCR), by twin screw extrusion (TSE), in the complete absence of solvent.

Mechanochemistry can be employed to carry out chemical reactions whilst eliminating or reducing the use of solvents, thereby making chemical synthesis less hazardous and more economical.[1] Recently, this form of synthesis has been scaled up from batch ball milling experiments (typically ghr^{-1} scale) to continuous processing using extrusion ($kghr^{-1}$ scale) (Figure 1).[2] Extrusion is an umbrella term used to describe a family of techniques that involve the conveying of material through a confined space. As a result, both shear and compressive forces are applied to the material, which can in turn instigate chemical reactions and drive them to completion.[3] Initially, Paradkar *et al.* reported the use of Hot Melt Extrusion (HME) for the formation of co-crystals.[4] Subsequently, we have reported the use of Twin Screw Extrusion (TSE) for the manufacture of Metal Organic Frameworks (MOFs)[5] and Deep Eutectic Solvents (DESs).[6] Due to the noted advantages of employing TSE for the synthesis of high quality materials, that in most cases did not require post process purification, we recently extended the technique successfully to four types of organic condensation reaction (Knoevenagel condensation, imine formation, Michael addition and Aldol reaction) which were successfully carried out by TSE. In addition, the Michael addition was found to be chemoselective under these conditions.[7]

Herein, we report that multiple sequential reactions can be telescoped together into a single extrusion process. Reaction telescoping in general can have significant benefits as noted already in solution-based Continuous Flow Technology.[8] In particular we demonstrate the synthesis of a nitrile followed by a subsequent Michael addition. Furthermore, we demonstrate that such reactions can alternatively be combined into a single multi-component process, which is arguably more efficient than telescoping. This has also been demonstrated through two further examples, one of which is the Petasis reaction, the first organic non-condensation reaction to be conducted by TSE.

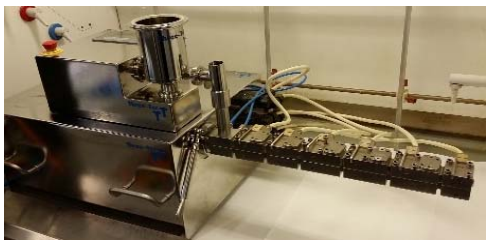

Figure 1: Laboratory scale 12 mm, 40:1 L/D Twin Screw Extruder that fits into a standard fume cupboard.

The system we chose to investigate as a telescoping process was a domino Knoevenagel condensation-Michael addition. Kaupp *et al.* have previously reported these reactions as a two-step ball milling process, carried out in the absence of solvent.[9] The conditions for the Knoevenagel condensation between vanillin and malononitrile, to produce **1**, were established in our previous work (120 °C and a screw speed of 55 rpm (Scheme 1).[7] Na_2CO_3 (0.1 mol. eq.) was also required to prevent the polymerisation of malononitrile.

Initially, each reaction was optimised individually. In each extrusion process, temperature can be varied along the length of the extruder barrel but the screw speed will of course be constant along the barrel. A screw speed of 55 rpm had been determined to be optimal for the Knoevenagel condensation,[7] and was therefore also applied to the Michael addition. The required reaction temperature for the Michael addition

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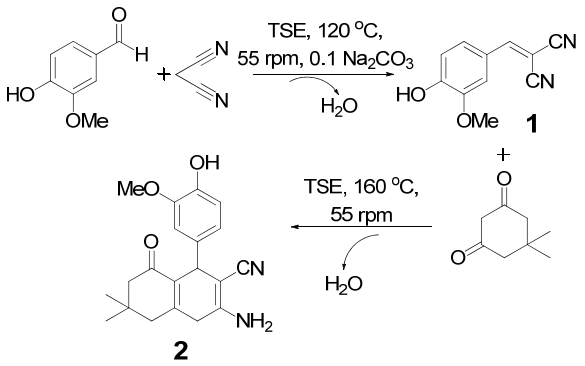
between 2-methoxy-3-hydroxybenzylidene malononitrile (**1**) (prepared by TSE) and dimedone to produce **2** was then investigated (Scheme 1). Temperatures between 25 °C and 160 °C were scoped and the degree of conversion to product was determined by ^{1}H NMR spectroscopy.



Scheme 1: Telescoped Knoevenagel condensation and Michael addition to form **2**.

Product was only observed to form when the temperature of the barrel was heated to 140 °C and a complete reaction was only achieved at 160 °C. As the melting point of dimedone is 147-150 °C, it is assumed that the formation of a melt is essential for the reaction to go to completion. **2** was thereby obtained as a fine yellow powder in an analytically pure form, since the water by-product was lost as steam at the reaction temperature.

We then attempted to telescope the Knoevenagel and Michael reactions together into a single process. In order to introduce the solid reagents into the extruder barrel, two solid twin-screw volumetric feeders were used, each equipped with an agitator to prevent settling of the reactant powders (Figure 2), and which could potentially be connected to any of the six ports along the extruder barrel. Solid Feeder A, connected to the first barrel port, contained a 1:1:0.1 molar mixture of vanillin, malononitrile and Na_2CO_3, whilst solid Feeder B, connected to the fourth port was charged with dimedone. The Knoevenagel condensation would thus be carried out in the first half of the barrel and the Michael addition in the second half.

Figure 2: Twin screw extruder, consisting of six heating sections with two attached volumetric feeders (A and B).

Sections 1-3 were heated to 120 °C (optimum for the Knoevenagel condensation[7]) and sections 4-6 to 160 °C (optimum for the Michael addition). The screw speed was set at 55 rpm and the screw configuration consisted of conveying and kneading segments (Figure 3). The overall configuration is customisable and so can be modified depending on the process being investigated. The kneading elements, which are most commonly employed in TSE processes, can be placed at angles of 30, 60 or 90°, depending on the amount of shear required (90° segments resulting in the greatest shear). Angles of 30 and 60° were deemed sufficient for this reaction..

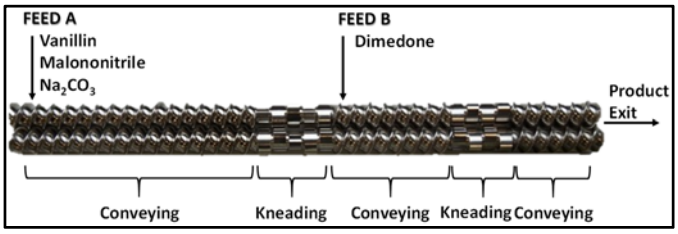


Figure 3: Standard screw configuration made up of conveying and kneading segments.

The mixture of vanillin, malononitrile and Na_2CO_3 were fed into the extruder at a rate of 223.2 ghr^{-1} whilst dimedone was fed in subsequently at a rate of 187.2 ghr^{-1} (calculated to provide the correct stoichiometry). However it was found very quickly that there were two problems with this set-up:

i) The reagents were found to 'bridge'[3] at the throats of both volumetric feeders as a result of the high temperatures employed in sections 1 and 4 (due to the melting and subsequent solidification of the reagents), blocking entry into the extruder, thereby preventing further addition of material into the barrel.

ii) The reaction mixture took a long time (40 minutes) to pass along the length of the barrel, during which time the torque (applied twisting force) fluctuated uncontrollably. This was found to be a result of a change in rheology of the mixture upon reaction, forming a viscous material that was difficult to convey along the screws.

In order to overcome problem (i), the first feeding section was kept at room temperature and the barrel heated to 120 °C for sections 2 and 3 towards Feeder 2, where the temperature was then increased to 135 °C (previously 160 °C). As a result, material did not melt in the feeder throats meaning that 'bridging' no longer occurred, and the reagents were fed in smoothly as powders.

Regarding problem (ii), when material is difficult to convey along an extruder barrel, increasing the screw speed typically overcomes this issue as more mechanical energy is being applied to turn the screws faster and convey the extrudate

more efficiently.[10] However, as the Knoevenagel condensation was found to proceed best at 55 rpm, we were reluctant to change this parameter in case it inhibited the reaction from proceeding to completion. Instead, we reduced the feed rates so that there was less material to convey along the extruder barrel. This successfully resolved the issue and the feed rates were changed to 192.4 ghr^{-1} (Feeder A) and 158.8 ghr^{-1} (Feeder B).

Thus, at a screw speed of 55 rpm and barrel temperature increasing from *ca.* 25 °C to 160 °C, a Knoevenagel condensation and a subsequent Michael addition were telescoped into a solvent-free continuous process, resulting in complete conversion to **2**. The optimised process had a throughput rate of 154.0 ghr^{-1}. The Na_2CO_3 was not removed from the final bulk product. ^{1}H NMR spectroscopy and CHNS elemental analysis indicated that (allowing for the presence of Na_2CO_3) an analytically pure product was formed (Figure 4). Post process purification could be carried out to remove Na_2CO_3 by doing a simple water-wash.

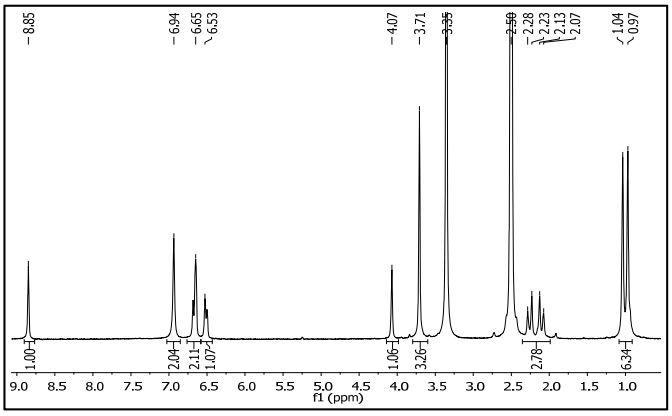
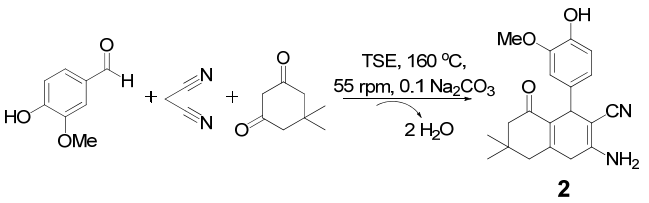


Figure 4: ^{1}H NMR spectrum (in d^6-DMSO) of the Knoevenagel condensation – Michael Addition telescoped reaction.

After telescoping two reactions involving four starting reagents, it was then investigated whether both reactions could be carried out simultaneously as a multi-component reaction, with all reagents added simultaneously via Feeder A (Scheme 2). This would eliminate the need for a second feeder and simplify the process still further.



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Scheme 2: MCR reaction of vanillin, malononitrile and dimedone in the presence of Na_2CO_3 (0.1 mol. eq.).

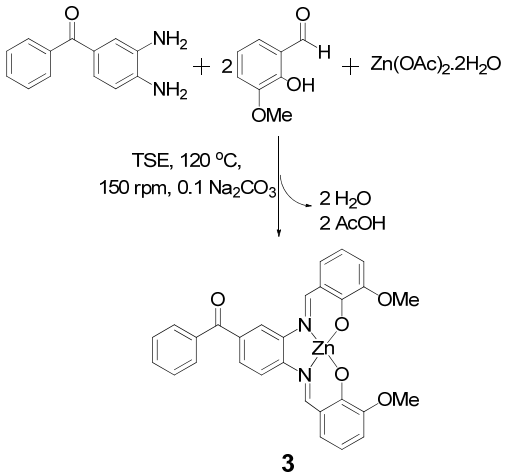
The reagents were conveyed along the extruder barrel at a range of different temperatures and screw speeds. At room temperature, the reaction did not initiate, even after passing through the extruder three times. However at a temperature of 140 °C, conversion to product was observed to be > 90 % (confirmed by ^{1}H NMR spectroscopy). In order to reach 100 % conversion to product, a temperature of 160 °C was required.

At 160 °C, screw speeds of 30 – 250 rpm were investigated, and for all experiments, conversions to product of greater than 94 % were achieved. At the highest screw speed of 250 rpm, greater shear is applied,[3] but this also reduces the residence time to a few seconds which is not always sufficient for a complete reaction. ^{1}H NMR spectroscopy showed that complete conversion to product occurred at a screw speed of 55 rpm.

The feed rate of this process was optimised to 372 ghr^{-1} giving a throughput rate of 160 ghr^{-1}, and a Space Time Yield (a measure of process efficiency) of 80 x 10^3 $kgm^{-3}day^{-1}$. Therefore, remarkably 80 kg of **2** could potentially be manufactured per day by this method, employing a laboratory-sized extruder which fits into a standard fume cupboard, suggesting that on an industrial scale, this technique has potential to synthesise tonnes of material per day. Allowing for the presence of a small amount of Na_2CO_3, which was not removed by washing, **2** was obtained in an analytically pure form as confirmed by ^{1}H NMR spectroscopy and CHN elemental analysis. Water, the only by-product of the reaction, was driven off as steam as a result of the high temperatures employed.

A second example of a MCR reaction carried out by TSE involved the formation of a Schiff base which was subsequently complexed with zinc (Scheme 3). The Schiff base could not be prepared in the absence of a metal salt, and therefore telescoping these reactions was not possible. Furthermore, a base was required to drive the reaction to completion. Initially Et_3N was used, however the less toxic Na_2CO_3 was found to work equally well.

Scheme 3: MCR reaction to produce a zinc complexed Schiff base, **3**



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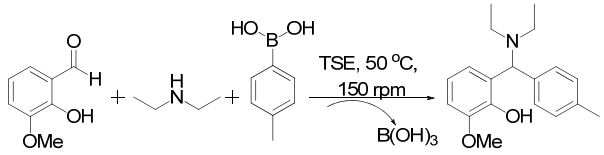
After investigating the effect of temperature (varying from room temperature to 160 °C), 100 % conversion to product was achieved at 120 °C (at screw speed of 55 rpm). At this temperature, complete reactions were only achieved at screw speeds ≤ 150 rpm, resulting in a residence time of *ca.* 45 seconds. Therefore, at 120 °C and 150 rpm, the optimum feed rate was 345 ghr^{-1} resulting in a throughput rate of 128 ghr^{-1} (STY of 63 x 10^3 $kgm^{-3}day^{-1}$). An analytically pure product (allowing for the presence of Na_2CO_3) was obtained as determined by ^1H NMR spectroscopy and CHN analysis.

Our final example of a MCR reaction was the Petasis reaction. This is a three component reaction between 4-methylbenzene boronic acid, diethylamine and *o*-vanillin (Scheme 4) which has not previously been demonstrated mechanochemically. This is also the first example of a non-condensation reaction by TSE, which could be significant in that the elimination of a by-product as a way to favour the reaction is not possible.



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Scheme 4: The Petasis reaction between *o*-vanillin, diethylamine and 4-methylbenezene boronic acid, forming **4**.

Experiments employing the standard screw configuration (Figure 3) were unsuccessful, with only partial conversion to product being observed (< 20 %). However, the conversion to product improved greatly when the screw configuration was customised to include kneading segments at 90° and a series of reverse segments (known to retard the flow of material along the barrel), which resulted in prolonged mixing and high shear kneading (Figure 5). After investigating both temperature and screw speed, a complete reaction was achieved at 50 °C (boiling point of diethylamine is 55 °C) and 150 rpm (using the setup in Figure 6). The residence time for this extrusion process was 7 minutes and the optimum feed rates were found to be 181.7 ghr^{-1} for the solid reagents and 65.1 $mlhr^{-1}$ for diethylamine. This gave a throughput rate of 184.6 ghr-1 and a STY of 92 x 10^3 $kgm^{-3}day^{-1}$.

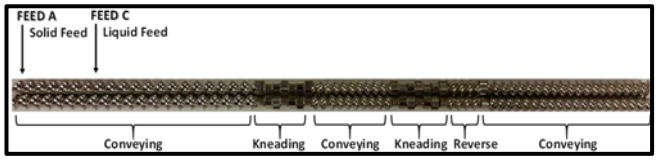

Figure 5: Alternative screw configuration employed, containing reverse conveying segments, employed for the Petasis reaction.

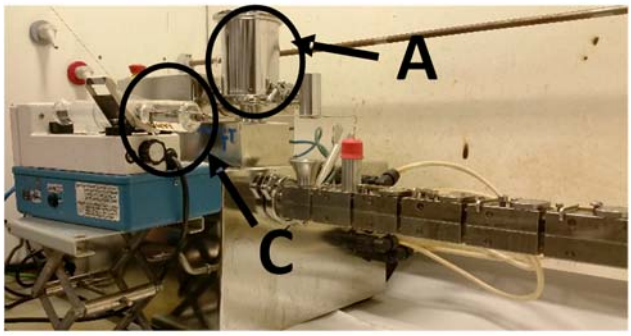

Figure 6: Twin screw extruder with a volumetric feeder (**A**) (feeding *o*-vanillin and 4-methylbenezene boronic acid), and a syringe pump (**C**) (feeding diethylamine) attached.

Boric acid is the by-product of this Petasis reaction, and to remove this, the extrudate was dissolved in ethyl acetate and washed with water. An analytically pure orange solid was isolated, as confirmed by ^1H NMR spectroscopy and CHNS elemental analysis.

In summary, we have demonstrated that multi-step chemical synthesis can be telescoped into a single solvent-free, continuous process by employing TSE. Furthermore, synthesis can be made even simpler by carrying out several reaction steps simultaneously, as shown by three multi-component reactions, including the Petasis reaction, which is the first non-condensation reaction carried out by TSE. It must also be noted that in each case, the effect of temperature alone was investigated as part of our control experiments, and did not lead to a substantial conversion to product. This confirmed that in each case mechanical agitation was required.

Acknowledgements

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